Azelastine Hydrochloride and Fluticasone Propionate in the Alleviation of Allergic Rhinitis

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Abstract: Allergic rhinitis is a global health problem. Although it does not endanger the life of patients with allergic rhinitis, its symptoms, such as rhinorrhea, sneezing, nasal itching, and nasal obstruction, can seriously affect the patients' quality of daily life and cause an economic burden to individual and country. In this paper, I summarize the pathology of allergic rhinitis, as well as introduce three classes of drugs used to treat allergic rhinitis, which includes corticosteroids, H1 receptor antagonists, leukotriene receptor antagonists. Among them, azelastine hydrochloride and fluticasone propionate are taken as examples to introduce their respective targets and specific pharmacological effects when contrasting H1 receptor antagonists and corticosteroids. The reasons why corticosteroids became first-line drugs and their limitations are elaborated.

1 INTRODUCTION

Allergic rhinitis is a nasal symptomatic disease caused by nasal mucositis after allergen exposure.

It belongs to type I hypersensitivity reactions(Vaillant et al 2020) and contains an early-phase and late-phase allergic response (Sin, Togias 2011, Min 2010). The hallmark of allergic rhinitis is nasal congestion, which often causes sleep disturbances in patients. Approximately one-quarter of 2500 adults in America reported that they would wake up or be unable to sleep at night because of the symptoms in a research in 2012(Meltzer et al 2012). A survey of 35757 families in the United States reported sleep disruption due to nasal allergic symptoms in up to 45% of children in 2009(Meltzer et al 2009). This phenomenon leads to mental fatigue and low mood of people. It also causes cognitive impairment, depression, and anxiety in patients by the combination with other symptoms, which leads to a decrease in work productivity of adults, and learning disabilities of children, an inability of children to get along better with their peers. As a result, there is a negative impact on patients' quality of life (Meltzer, 2001, Muñoz-Cano R et al 2018).

2 THE DISEASE

2.1 Significance in China and Other Countries in the World

Allergic rhinitis is a common disease that affects up to 40% of the global population with about 23% to 30% of Europeans with a prevalence of 25% in Sweden in 2012 (Bauchau, Durham 2004), and 12% - 30% of the population in the United States (Nathan et al 2008). People with allergic rhinitis are obliged to ease their symptoms by using medicines. For example, in 2017, fluticasone propionate that is a drug to alleviate symptoms of allergic rhinitis was the 15th most commonly prescribed medication in the United States, with more than 32 million prescriptions (up from 16th place & 29 million in 2016). In 2018, azelastine hydrochloride that is also a drug to alleviate symptoms of allergic rhinitis was the 240th most commonly prescribed medication in the United States, with more than 2 million prescriptions. The prevalence of allergic rhinitis is increasing globally (Dykewicz, Hamilos 2010). It is usually a long-standing disease and often goes unnoticed by people due to its high universality of symptoms at its initial stage. Although it is not life-threatening, its symptoms are often bothersome and reduce the quality of life and work of people, and it also causes a significant burden on the individual and the country

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(Canonica et al 2007). The burden on society is the costs associated with the treatment of allergic rhinitis (Simoens, Laekeman 2009). Although the direct cost of treating allergic rhinitis is not obvious, it incurs substantial indirect costs (Bousquet et al 2008).

In 2016, the total cost of allergic rhinitis was estimated at € 1.3 billion per year in Sweden, which has a population of 9.5 million people. The total cost per person per year due to allergic rhinitis was € 961.1, which includes mean direct and indirect costs of € 210.3 and € 750.8, respectively in Sweden(Cardell et al 2016)]. In Germany, the total cost of allergic rhinitis was € 240 million in 2000, which included both direct and indirect costs (Bachert et al. 2006). It is difficult to search the prevalence of allergic rhinitis in China in recent years because of the paucity of relevant data on allergic rhinitis. According to the data of The National Bureau of Statistics of China, China had a population of 1.37 billion at the end of 2014. The prevalence of allergic rhinitis reported in 18 major cities in China was 17.6%.

The overall prevalence in the four major cities of Western China (Chengdu, Chongqing, Nanning, and Urumqi) is 34.3%, 34.3% in Chengdu, 32.3% in Chongqing, 30.3% in Nanning, and 37.9% in Urumqi (Figure 1). The overall prevalence of allergic rhinitis in several areas in northern China (rural areas of Qingxian, Hebei; coastal fishing village of Bohai Bay, Huanghua; area of Wuling Mountain, Chengde; urban areas of Tianjin) are about 9.2% (Zhang, Zhang 2014). This preliminary suggests that different geographical and climatic contribute to the differences in prevalence. Meanwhile, occupational factors are also considered as one of the reasons for the different prevalence. For example, farmers have a 2.32-fold increased risk (Wang et al 2011, 2012). Although there is variation in prevalence across regions, the prevalence has generally increased in both adults and children over the past 20 years. The epidemic trends of allergic rhinitis in China and the trends of other developing countries are the same.

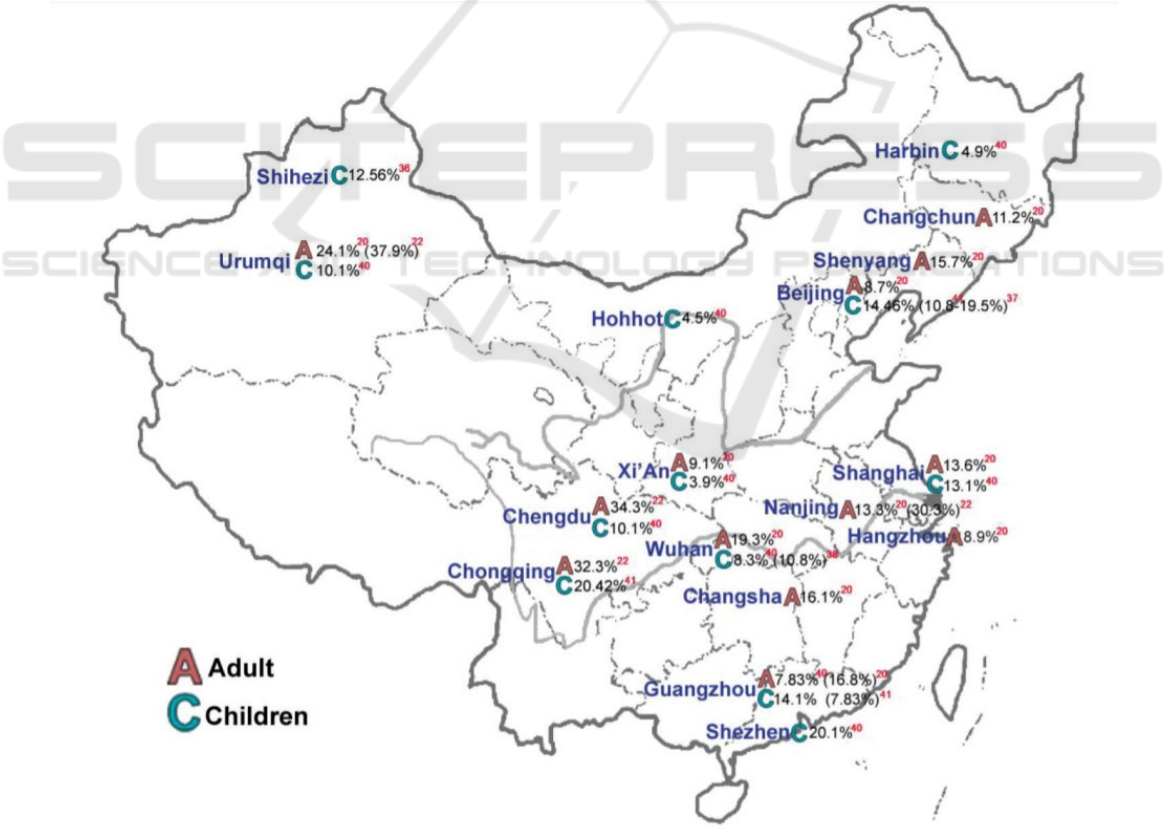

Figure 1: Prevalence of allergic rhinitis in adults and children in different cities in China in 2008 (Zhang, Zhang 2014)].

2.2 The Pathology of Allergic Rhinitis and Its Symptoms

Antigens that cause hypersensitivity reactions are called allergens, which contain certain drugs, plant pollen, dust mites, fungal spores, animal dander or feathers, insects or their venoms as well as foods, such as fish, shrimp, eggs, milk, and certain enzymes classes, such as subtilisin.

When the allergens enter the human body, they stimulate B-lymphocytes to convert into plasma cells which can produce immunoglobulin E (IgE) antibodies. IgE is found at very low levels in normal human serum and is significantly increased in the serum of hypersensitive patients, so it is often considered by doctors as an important indicator for the diagnosis of allergic diseases (Ansotegui et al. 2020).

IgE has a high affinity for basophils and mast cells, so they can bind to high-affinity IgE receptors (FcεRI) on the surface of tissue mast cells and blood basophils (Turner, Kinet 1999). When there is a reappearance of the same allergen and cross-links to IgE on the cell surface, FcεRI activates mast cells or basophils by signal transduction and releases intragranular active mediators, such as histamine, kinins, proteases, chemokines, and heparin (Siraganian 2003), and several types of type 2 cytokines like interleukin (IL)-3. This process is called degranulation (Figure 2), which is the feature of the early-phase reaction (Figure 3). At the same time, arachidonic acid is released from cell membrane phospholipids of activated mast cells and basophils, then it is catalyzed by lipoxygenases or cyclooxygenases to form the inflammatory lipid mediators that include leukotrienes (composed of LTC4, LTD4, and LTE4) and prostaglandins, respectively (Moon, Befus, Kulka 2014). Symptoms triggered by histamine-mediated anaphylaxis and inflammatory mediators in the early-phase response include bronchoconstriction, vasodilation, smooth muscle contraction, etc.

Late-phase allergic responses (Figure 3) appear several hours after exposure to the allergen. The responses are characterized by the cellular recruitment of basophils, neutrophils, T-lymphocytes, monocytes, and eosinophils. They can release several mediators, including cytokines, prostaglandins, and leukotrienes, which increase the duration of the inflammatory response (Sin, Togias 2011, Min 2010). This means that the late-phase response is related to the development and persistence of tissue edema and nasal congestion.

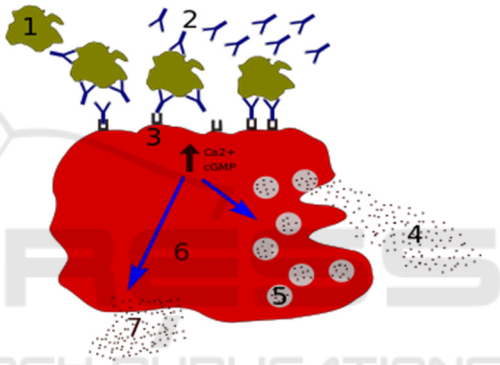

Figure 2: Degranulation processes 1 - antigen; 2 - IgE antibody; 3 - FcεRI receptor; 4 - preformed mediators (histamine, proteases, chemokines, heparin); 5 - granules; 6 - mast cell; 7 - newly formed mediators (prostaglandins, leukotrienes).

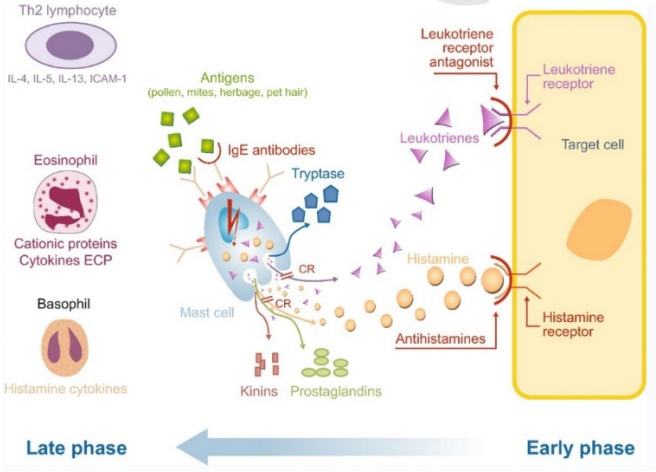

Figure 3: Early-phase and late-phase allergic response of allergic rhinitis (Bjermer, Westman, Holmström, Wickman 2019).

The main symptoms of patients with allergic rhinitis are runny nose, sneezing, nasal itching, and nasal congestion, it is usually accompanied by ocular pruritus, redness, and/or lacrimation in 60% - 70% of patients (Canonica et al 2007, Bousquet et al 2008, Schatz 2007). Subsequent disease development may lead to related conjunctivitis, postnasal drip, eustachian tube dysfunction, otitis media, etc. At the same time, about 20% - 50% of patients with allergic rhinitis suffer from clinical asthma (Strachan et al 1997), which shows allergic rhinitis often coexists with asthma.

2.3 Drugs Used to Treat the Disease and Their Origins

There are three categories of drugs that are used to treat allergic rhinitis. They have different modes of action and different interactions in allergic rhinitis cases.

a) H1 receptor antagonists

The first-generation of H1 receptor antagonists (Figure 4), diphenhydramine (Benadryl), carbinoxamine (Clistin), clemastine (Tavist), chlorpheniramine (Chlor-Trimeton), and brompheniramine (Dimetane) that were marketed before the 1980s (Berdy et al 1991, Welch et al 2002) can cross the blood-brain barrier and enter the central nervous system because of their high lipid solubility, which causes the side effects of central depression and sedation(Kay 2000). At the same time, the selectivity to the H1 receptor of the first generation of H1 receptor antagonists is not strong enough (Kalpaklioglu, Baccioglu 2012), so there are the side effects, such as anti-cholinergic, anti-adrenergic, analgesic effects (Ali Habibi ETR 1991).

Second-generation H1 receptor antagonists (Figure 4), such as cetirizine, terfenadine, astemizole, loratadine, azelastine, and acrivastine (Aaronson 1991), were invented to overcome these side effects as much as possible. They are more hydrophilic and less lipophilic, and they also have a higher selectivity for the H1 receptor, which means that the possibility of the drugs crossing the blood-brain barrier is greatly reduced and the central side effects are attenuated compared with the first generation of H1 receptor antagonists (Kay 2000).

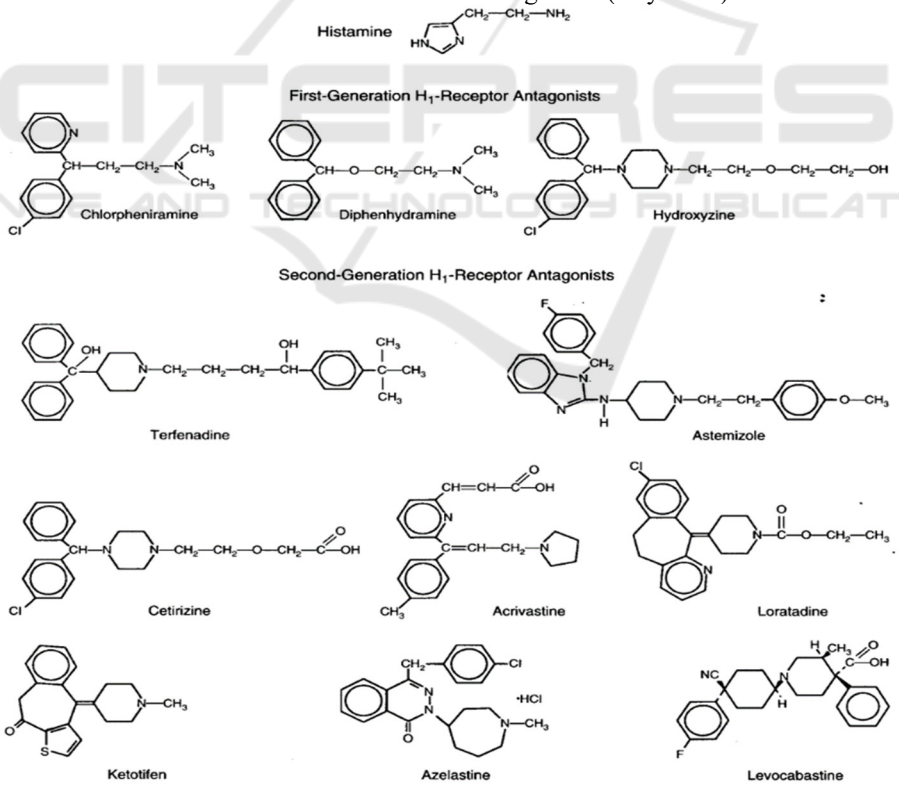

Figure 4: Chemical structures of H1 receptor antagonists (Simons, Simons 1994) The treatment of allergic rhinitis generally requires intranasal and oral H1 receptor antagonists. After oral administration, the concentration of the drug in the nasal cavity often cannot reach the effective value (Molimard, Diquet, Benedetti 2004, Urien et al 1999), so it is necessary to increase the concentration through intranasal injection (Horak, Zieglmayer 2009).

b) Corticosteroids

Corticosteroids are considered a safe and effective first-line treatment for allergic rhinitis, although it was initially reserved as a second-line agent (Group IRMW 1994). Several intranasal corticosteroids are available for allergic rhinitis (Figure 5), such as beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide (Trangsrud, Whitaker, Small 2002). The following contents include the relationships of structure-activity of corticosteroids.

The carbon skeleton of each corticosteroid consists of three 6-carbon rings (rings A, B, and C) and one 5-carbon ring (ring D). Common features among each other are the ketone oxygen group at position 3, unsaturated double bond between carbons 4 and 5, hydroxyl group at position 11, and a ketone oxygen group on carbon 20. The changes at positions 16, 17, and 21, outside the D-loop, are the largest differences between the individual molecules (Szefler 2001).

For example, the furoate group of mometasone furoate can enhance the molecular affinity to the glucocorticoid receptor binding site. Other groups improve the activity of corticosteroid compounds.

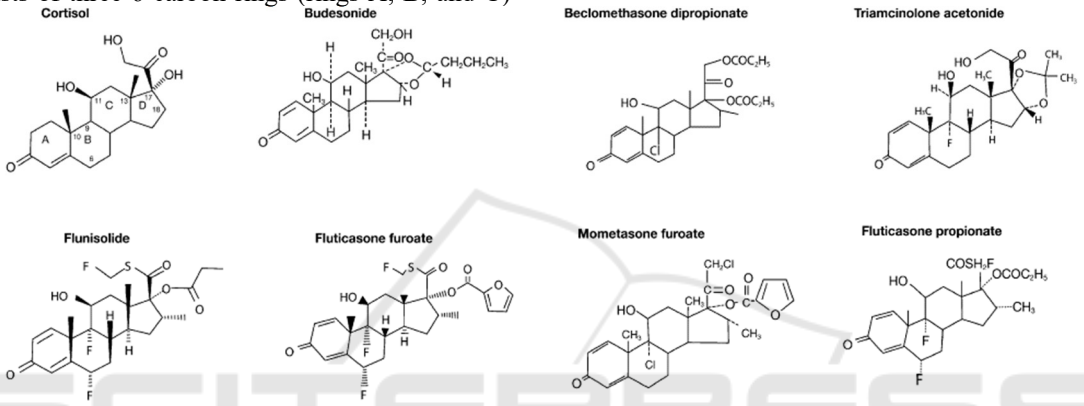

Figure 5: Chemical structures of corticosteroids.

Modes of administration include intranasal administration and systemic administration. The common way is intranasal administration because anti-inflammatory effects of the drugs can be problematic if systemic concentrations of these drugs are excessive, and intranasal administration can achieve the efficacy of systemic administration while minimizing side effects by oral administration for patients with allergic rhinitis (Pichler, Klint, Blaser, Graf, Sauter, Weiss et al.1988).

c) Leukotriene receptor antagonists

Leukotriene receptor antagonists, such as montelukast, zafirlukast, and pranlukast, can block the activity or secretion of cysteinyl leukotriene (CysLT) that is an inflammatory mediator and include leukotriene C4(LTC4), leukotriene D4(LTD4), and leukotriene E4(LTE4) (Peters-Golden, Henderson 2005). There are two ways to block the action of leukotrienes. The first way is to inhibit the synthetic pathway of leukotriene metabolism by inhibiting 5-lipoxygenase. The second way is to rely on the antagonistic effect of drugs on cysteinyl-leukotriene type 1 (CysLT1) receptors, such as montelukast and zafirlukast, which can block the effect of CysLT on CysLT1 receptor of target cells, such as bronchial smooth muscle. Therefore, it can alleviate the symptoms of allergic rhinitis (Singh 2013).

3 AZELASTINE HYDROCHLORIDE AND FLUTICASONE PROPIONATE

3.1 Basic Information on Azelastine Hydrochloride and Fluticasone Propionate

a) Azelastine hydrochloride

The IUPAC name of azelastine hydrochloride is 4-[(4-chlorophenyl)methyl]-2-(1-methylazepan-4-yl)phthalazin-1-one;hydrochloride. 'Hydrochloride' means that it is the hydrochloride salt of azelastine.

The molecular formula of azelastine hydrochloride is C22H24ClN3O.HCl. Figure 6 and figure 7 show the chemical structure of azelastine hydrochloride.

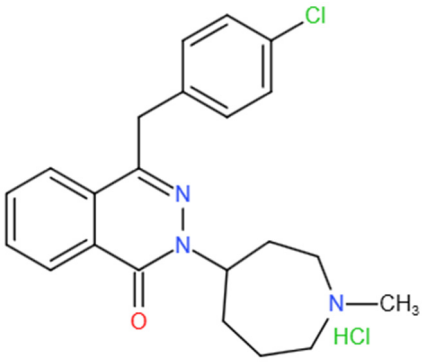

Figure 6: Chemical structure of azelastine hydrochloride (2D).

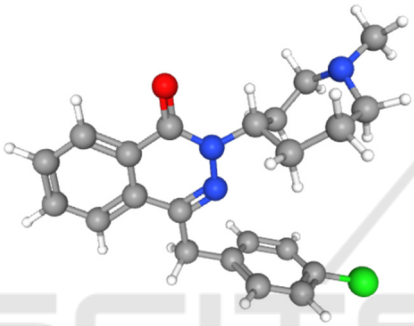

Figure 7: Chemical structure of azelastine (3D).

Azelastine hydrochloride is a racemic mixture with a melting point of 225°C, so it is a white crystalline powder at room temperature with a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol, and slightly soluble in ethanol, octanol, and glycerine. It is sold as a form of the solution under the brand name Optivar.

b) Fluticasone propionate

The IUPAC name of fluticasone propionate is [(6S,8S,9R,10S,11S,13S,14S,16R,17R)-6,9-difluoro-17-(fluoromethylsulfanylcarbonyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate. Fluticasone Propionate is the propionate salt form of fluticasone.

The molecular formula of fluticasone propionate is C25H31F3O5S. Figure 8 and figure 9 show the chemical structure of fluticasone propionate.

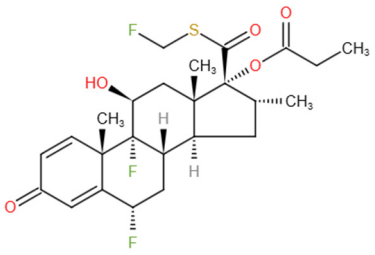

Figure 8: Chemical structure of fluticasone propionate (2D).

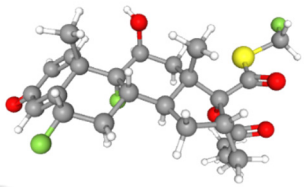

Figure 9: Chemical structure of fluticasone propionate (3D).

The melting point of fluticasone Propionate is 261-273 °C, so it is solid at room temperature with a molecular weight of 500.6. It is insoluble in water and sold under the brands of Flovent and Florase. So, it is not easy to dissolve in human bronchial fluid, the deposition of drugs in the airways increases. The release of drugs is slower, and the local action time is longer.

3.2 Pharmacology of Azelastine Hydrochloride and Fluticasone Propionate

a) Azelastine hydrochloride

H1 histamine receptors belong to the family of rhodopsin-like G-protein-coupled receptors. They are activated by histamine and are expressed in smooth muscles, vascular endothelial cells, the heart, and the central nervous system. It can trigger anaphylaxis mediated by histamine.

In the type Ⅰ hypersensitivity allergic reactions process, once histamine is released from mast cells or basophils by cellular degranulation, it can bind to H1 histamine receptors to initiate allergic reactions (Lytina et al 2002, Tamaoki et al 1999). Azelastine

hydrochloride is useful in the treatment of allergic rhinitis by competing with histamine for H1 histamine receptors (Figure 10).

Therefore, histamine-mediated symptoms of anaphylaxis, such as rhinorrhea, itching, and sneezing are reduced. This drug also has the effects of stabilizing mast cells, anti-leukotrienes, and anti-inflammatory (Horak, Zieglmayer 2009).

Azelastine hydrochloride can effectively block the calcium channel regulated by IgE in the degranulation process of mast cells and stabilize mast cells, so it can prevent the release of histamine and other mediators, such as prostaglandins, kinin, and interleukin (Van Hoecke, Vandenbulcke, Van Cauwenberge 2007, Kempuraj et al 2003).

Azelastine hydrochloride can inhibit phospholipase A2 and LTC4 synthase and prevents the release of leukotriene (LTB4 and LTC4) by stabilizing mast cells (Hamasaki et al. 1996).

Anti-inflammatory properties of azelastine hydrochloride are resulted from inhibiting the release of inflammatory cells and mediators. These include eosinophils and neutrophils as well as mediators.

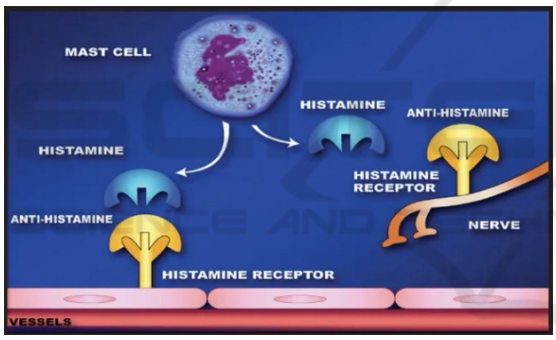

Figure 10: The process of preventing mast cell degranulation.

b) Fluticasone propionate

The glucocorticoid receptor (GR) is the receptor to which cortisol that is the endogenous glucocorticoid hormone and is produced in many animals, mainly by the zona fasciculata of the adrenal cortex in the adrenal gland (Thau, Gandhi, Sharma. Physiology, cortisol. 2019.), and other glucocorticoid receptor agonists (GC) bind. It is expressed in almost every cell in the body. When cortisol or GC bind to GR, it achieves anti-inflammatory effects by regulating gene transcription (Lu et al 2006, Rhen 2005).

Glucocorticoid receptor agonists that have often been used to treat allergic rhinitis belong to corticosteroids. Fluticasone propionate, one of the glucocorticoid receptor agonists (GC molecules), binds to and activates glucocorticoid receptors (GR), thereby activating lipocortins. Lipocortins can inhibit cytosolic phospholipase A2 that can trigger a cascade of responses involved in the synthesis of inflammatory mediators, such as prostaglandins and leukotrienes. The transcriptional activity of nuclear factor kappa-B(NF-κB) is blocked, thereby inhibiting the transcription of cyclooxygenase 2, which is essential for the production of prostaglandin.

The complex formed from binding the molecules of fluticasone propionate to GR can alter transcriptional activity (Figure 11), which leads to decreased expression of proinflammatory molecules and cells, including Langerhans cells, lymphocytes, mast cells, basophils, and eosinophils, and inhibits the arrival of Langerhans cells, macrophages, mast cells, T-lymphocytes, and eosinophils in the nasal mucosa (Holm et al 2001). At the same time, it increases anti-inflammatory molecules and β-expression of adrenergic receptors (Mygind et al. 2001).

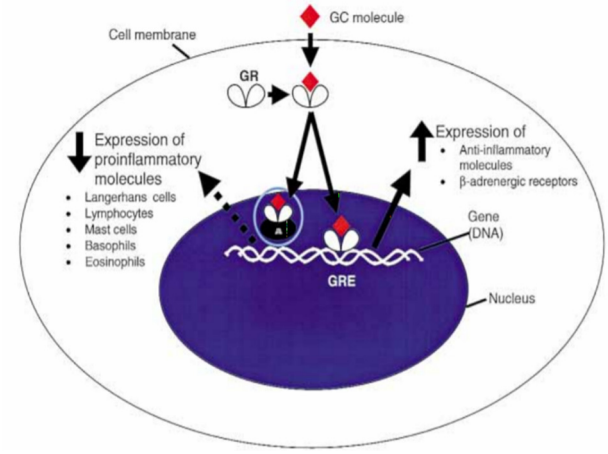

Figure 11: Actions of glucocorticoid (GC) molecule in the inflammatory process (Mygind et al. 2001).

c) Compare azelastine hydrochloride and fluticasone propionate

Table 1: The differences between azelastine hydrochloride and fluticasone propionate.

	azelastine hydrochloride	fluticasone propionate
Targets of drug	H1 histamine receptors on the target cell.	The glucocorticoid receptors on the target cell.
Functions	Compete with histamine for H1 histamine receptors. Effects of stabilizing mast cells, anti-leukotrienes, and anti-inflammatory.	Bind to and activates glucocorticoid receptors, thereby activating lipocortins and reducing the production of inflammatory mediators. Alter transcriptional activity, that leads to decreased expression of proinflammatory molecules and cells, an increase in expression of anti-inflammatory molecules, and β-expression of adrenergic receptors.

The different pharmacology of the two drugs has led to different therapeutic effects (see Table 1). Most patients with allergic rhinitis who present to a primary care physician have moderate to severe symptoms, the use of fluticasone propionate is a better option (Bousquet et al. 2003) because fluticasone propionate is a potent inhibitor of anaphylaxis in the late phase of allergic rhinitis. They are more effective to control the symptoms of allergic rhinitis, including nasal congestion, and rhinorrhea than leukotriene receptor antagonists than H1 receptor antagonists (Weiner, Abramson, Puy 1998). However, it is important to note that intranasal corticosteroids are best initiated before exposure to relevant allergens, as their peak effects may take several days to develop, necessitating their regular use to achieve better outcomes (Lee, Mace 2009).

4 CONCLUSION

This article has summarized the pathology of allergic rhinitis and its symptoms, its significance in China and other countries, and the current three classes of drugs to treat it. At the same time, azelastine hydrochloride and fluticasone propionate were used as an example to explain the targets and pharmacological effects of these two classes of drugs. Typically, the effects of intranasal corticosteroids are more obvious than those of second-generation antihistamines. It is worth noting that current medications only alleviate symptoms of allergic rhinitis. Finding any approach to the thorough treatment of allergic rhinitis is the direction of research in the future.

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